IS ANTIMICROBIAL RESISTANCE IN HOSPITAL MICROORGANISMS RELATED TO ANTIBIOTIC USE?*

JOHN E. MCGOWAN, JR., M.D.
Professor of Medicine and Pathology
Emory University School of Medicine
Atlanta, Georgia

THE frequency with which organisms causing nosocomial (hospital-associated) infection are resistant to antimicrobial agents has been a continuing concern to clinicians, microbiologists, and epidemiologists throughout the world.[1] Our ability to stay "one step ahead" of these pathogens is frequently threatened by their propensity to develop resistance to antimicrobial drugs in current use and to remain unaffected by newly-introduced agents.[2]

During the past decade, changes have occurred in the etiology of nosocomial infection.[3] Some pathogens in the hospital have developed resistance to antimicrobial drugs in current use and others have demonstrated immediate resistance to newly-introduced agents. Often, such resistance has characterized prominent hospital pathogens.[4]

Huge quantities of antimicrobials are prescribed each year in the United States.[2,5] In addition, the hospital environment itself is contaminated with antimicrobials as a result of their frequent administration.[6] Such extensive presence of antimicrobials must be considered a possible risk factor for emergence of resistant organisms.[1,2] This paper reviews some of the methodologic problems involved in studying this issue, examines the data for and against the existence of such a cause and effect relationship, and suggests areas for further investigation.

PROBLEMS WITH METHODS FOR STUDY OF RESISTANCE

Studies of this topic have been thus far hindered by problems with the methods used for investigation (Table I). Prominent among these are the following:

*Presented as part of a *Symposium on Bacterial Resistance: Exploring The Facts and Myths* held by The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine at the New York Academy of Medicine March 18, 1986.

TABLE I. PROBLEMS WITH METHODS USED FOR STUDYING ANTIMICROBIAL RESISTANCE IN HOSPITAL ORGANISMS

A. No consensus definitions for resistant or "multiresistant"

B. Selection biases:
   1. Clinician concern
   2. Marker makes study easier
   3. More editorial interest
   4. Small sample of hospitals
      a. Outbreaks predominate
      b. Relevance to community hospitals

C. Control of confounding variables
   1. Patient population
   2. Procedures and practices
   3. Organism distribution
   4. Patterns of antimicrobial use

D. Simultaneous use of multiple control efforts

Definitions of resistance and "multiresistance." There is a lack of consensus about the definition of a multiresistant organism. Some investigators have not even stated their definition; in other studies, drugs being considered and the number used to define multiple resistance have not been given. Varying definitions of "multiresistant" have been used in different reports. In general, three concepts have appeared.[7] One defines a multiresistant organism as one resistant to a specific number of drugs. A second approach describes a multiresistant organism as one resistant to "drugs usually employed." Finally, a third variant suggests that a multiresistant organism is one resistant to two or more drugs to which the bacterium "usually is susceptible."

The problem with these definitions is that they depend to some extent on subjective decisions about what constitutes "usual susceptibility." This well might vary from hospital to hospital, from organism to organism, and from investigator to investigator. The judgments may also change over time. For example, a strain of *Staphylococcus aureus* exhibiting resistance to penicillin might well have been the subject of study as a resistant organism in the 1960s, but now could be regarded as the "usual" organism in a hospital or community.

A second problem of definition is that laboratory techniques used to test for susceptibility vary from hospital to hospital. Since these vary from each other in specifications and procedures used, some variability may be introduced.[4]

Selection biases. Selection biases are likely in studies of this subject. These may take many forms.[7]

A resistant organism may cause more concern than a susceptible one to the clinician, who then may obtain more cultures of resistant strains. As a result, resistant strains might be overrepresented in the total processed by a laboratory.

Resistance to one or more antimicrobials can serve as a marker to identify a given strain. This may permit study of such a strain while other clinically important strains go unnoticed.

Reports of resistance problems may be more interesting to editors, leading to an overrepresentation in the literature of the impact of these strains.

A great deal of our knowledge of this subject comes from outbreaks. It is difficult to know whether the ecology of the organisms and their hosts in these special circumstances can be applied to nonepidemic settings. Extrapolation is especially difficult to community hospitals, as these seem to experience epidemics of nosocomial infection very rarely.[8]

Much of the information about resistant hospital organisms comes from their intense study at a small number of hospitals.[9] In these, local changes in patient population, types of medical care available, and other individual circumstances may influence the apparent trends of disease incidence. Thus, it is difficult to generalize to regional or national levels the epidemiologic patterns that are found.

Resistant hospital organisms apparently exist to a much lesser extent in community hospitals.[4,10-12] For example, one review of a large data base drawn primarily from smaller community hospitals has found little evidence of resistance or of increase in frequency of resistant organisms.[11] Likewise, national cooperative projects for surveillance of antimicrobial resistance[4,12] show resistance rates for community hospitals considerably less than those noted for the university and referral centers where most of the studies of resistance are done. Yet, increasing prevalence of resistance exists in a number of university and other referral centers.[13] Trends at Grady Memorial Hospital illustrate a gradual decrease in prevalence of resistance to some (but not all) of the commonly-employed drugs without marked change of organisms causing infection (Table II).

Control of confounding variables. Antimicrobial usage has often been assumed to be the sole factor responsible for changes in resistance patterns. However, a number of other factors can be involved as well (Table III). It is necessary to control for these confounding variables (i.e., pertinent fac-

TABLE II. CHANGES IN PREVALENCE OF RESISTANCE TO SELECTED ANTIMICROBIAL AGENTS IN GRAM-NEGATIVE AEROBIC BACILLI ISOLATED FROM BLOOD CULTURE, GRADY MEMORIAL HOSPITAL, 1983-1985

	Year		
	1983	*1984**	*1985*
Total isolates tested:	321	215	290
Percent of organisms susceptible to:			
Ampicillin	40%	44%	40%
Carbenicillin	55	60	59
Cephalothin	65	60	56
Cefamandole	84	81	77
Cefoxitin	79	76	74
Ceftizoxime**	93	92	89
Gentamicin	97	93	91
Tobramycin	97	93	92
Trimethoprim-Sulfamethoxazole	85	83	81
Organisms:			
Acinetobacter	4%	2%	4%
Enterobacter	10	9	10
E. coli	45	44	48
Klebsiella	21	18	15
P. mirabilis	6	9	9
Pseudomonas	7	9	8
Serratia	3	5	3
Other	4	4	4

*Nine-month sample
**Cefotaxime tested in 1983-1984; ceftizoxime tested 1985

TABLE III. FACTORS AFFECTING ANTIMICROBIAL RESISTANCE IN HOSPITAL ORGANISMS

Patients with compromised host defenses more prevalent in hospitals today
New procedures and techniques needed for modern care
Greater impact of community organisms
Inherent traits of organisms
Some drugs better able to elicit resistance than others
Antimicrobial use

tors other than antimicrobial use) before one can determine the precise role of antimicrobial agents as a risk factor or indicator.[14] Among factors important as possible sources of confounding, the following are especially prominent.

Changes in prevalence of patients with impaired host defenses. Development of new therapies and technology has allowed patients to live who for-

merly might have died of any of a number of diseases. These patients often have impaired host defenses against infection, either as a result of their diseases or the therapies given for them.[15] This relative susceptibility allows organisms of limited virulence (''opportunistic'' pathogens) to gain a foothold that would be impossible in the face of normal host response. While many of the opportunistic organisms are inherently resistant to commonly-used antimicrobials, they probably colonize these patients primarily because host defenses are weakened rather than because they can fend off antimicrobials.[9]

Infection of those with limited host defenses by opportunistic pathogens has been noted for many years. The increased frequency of such infections today may simply be because there now are more patients with such compromised defenses in our hospitals.[9] Prospective schemes for reimbursement enhance this trend by attempting to ensure that people who are only moderately ill are not admitted; the overall effect is to increase the average severity of the illness present in hospitalized patients.

Changes in procedures and techniques employed. New procedures and instruments are a part of modern hospital care. Some microorganisms have attributes that permit survival in or around these devices or equipment. These characteristics may be entirely independent of the organism's susceptibility or resistance to antimicrobials. For example, the prominence of *Providencia stuartii* as a pathogen in catheter-associated urinary tract infection appears to relate to a unique ability of the organism to survive in catheter materials, rather than to its known ability to resist several antimicrobials.[16]

Increased influence of organisms causing community-acquired infection and changes in their antimicrobial resistance. Hospital infection patterns are affected by the concurrent frequency and etiology of infections that hospitalized patients acquired in the community.[3] A high prevalence of infections in patients presenting for hospital admission adds to the ''organism burden'' of the hospital and increases potential reservoirs for hospital transmission. Prospective reimbursement has set a premium on early discharge from hospital. By doing so, it has increased the interchange of patients between hospital and community, and thus added to the influence of community organisms on the hospital.

Many organisms involved in community-acquired infection are more resistant to antimicrobials than in the past. A recent example of this is the development of non-enzyme-mediated resistance in the gonococcus, which also has developed beta-lactamase mechanisms of avoiding therapy during the past decade.[17] The importance of resistance in the community also is illustrated

by the finding of cefoxitin resistance in an appreciable number of gram-negative bacillary isolates from community-acquired bacteremia.[18]

Changes in inherent characteristics of the organism. Microorganisms are constantly changing in many ways, few of which seem related exclusively to antimicrobial therapy. Some seem to have attributes that affect virulence and their ability to persist in the hospital. For example, the ability to produce slime seems to enhance the ability of certain coagulase-negative staphylococci to be nosocomial pathogens, especially on catheters or other prosthetic devices.[19] The presence or absence of plasmids coding for certain characteristics appears to affect the likelihood of *S. aureus* persisting in the hospital environment.[20] Such factors may be more important in determining the course of infection than the presence or absence of antimicrobials, but we are unable to recognize more than a few of these inherent characteristics; when we cannot identify them we cannot control for them.

Variation in practices of drug use. All drugs are not equally likely to lead to superinfection or emergence of resistance.[21] Thus, the pattern of use in a given institution will have a great impact on resistance patterns.[2,7]

Use of multiple control efforts at the same time. Some studies report temporal associations between decreases in antimicrobial agent usage and lowering the prevalence of resistant organisms. Unfortunately, many of these episodes also include other "epidemic control" measures taken in addition to changing usage of antimicrobials.[22] In these reports it is unclear which was the crucial factor leading to the decreased frequency of resistant organisms.[14]

Evidence For A Causal Relationship

Seven types of evidence can be marshalled to link hospital antimicrobial usage and antimicrobial resistance in hospital bacteria (Table IV). These have been reviewed in detail previously,[7] and will be summarized here only briefly.

Antimicrobial resistance is more prevalent in bacterial strains causing hospital infection than in organisms from community-acquired cases. In outbreaks this has been shown repeatedly for a large number of different organisms.[7] However, this increased susceptibility has been documented infrequently for nonoutbreak periods, and rarely in community hospitals. Dixon[9] reviewed data from the Comprehensive Hospital Infections Project of the Centers for Disease Control, in which eight community hospitals were

TABLE IV. EVIDENCE THAT ANTIMICROBIAL USE IS RELATED TO RESISTANCE IN HOSPITAL ORGANISMS

A. *Consistent association*
1. Resistance is more prevalent in bacterial strains causing hospital infection than in organisms from community-acquired infection.
2. In outbreaks patients with resistant strains are more likely to have received prior antimicrobial therapy than are controls.

B. *Concomitant variation*
1. Changes in antimicrobial usage lead to parallel changes in prevalence of resistance.

C. *Dose-effect relationship*
1. Hospital areas having the highest usage of antimicrobials also have the highest prevalence of antibiotic-resistant bacteria.
2. An increasing likelihood of colonization or infection with resistant organisms occurs with increasing duration of exposure to antimicrobials in the hospital.
3. Increasing dosage of antimicrobials leads to greater likelihood of superinfection or colonization.

D. *Reasonable biological model*
1. Proposed cause precedes proposed effect.

surveyed. He found similar susceptibility patterns among nosocomial and community strains of *Staphylococcus aureus* and Gram-negative aerobic bacilli; the only significant differences between hospital and community strains were for *E. coli* and indole-positive Proteus, and in both cases hospital strains were more susceptible.

During outbreaks, patients with resistant strains are more likely to have received prior antibiotic therapy than are controls. This has been observed in a variety of outbreaks due to different bacteria,[7,23] and has been observed in studies of endemic disease.[10,17,24,25] The antimicrobial administered was not necessarily the one for which resistance was subsequently noticed; our increasing knowledge of the linkage of resistance determinants[13,20] suggests that these observations are plausible.

In the above studies antimicrobial usage may have served merely as a marker for sicker patients; it is hard to determine whether colonization by resistant organisms resulted from treatment or merely occurred because these were the most susceptible patients. Thus, these data, as those detailing prevalence of resistance in hospital versus community strains, suggest antimicrobials as a risk indicator for resistance, but do not necessarily establish a causal relationship.[7]

Changes in antimicrobial usage lead to parallel changes in prevalence of resistance. In a number of studies, increased use of antimicrobials led to in-

creased resistance, and decreased usage led to decreased resistance. Some studies have demonstrated both of these associations in the same patient population. Reports also have documented total lack of resistance before use of antimicrobials and subsequent development of resistance after specific antibiotics were introduced.[26]

In an earlier review, six studies in 1953 through 1979 detailing a temporal relationship between increased use of antimicrobials were listed, and 16 studies from the period 1953-1978 were cited showing decreased usage leading to decreased resistance.[7] Since then, papers illustrating this relationship have continued to appear;[24,25,27-53] they have dealt with a variety of drugs and microorganisms (Table V).

A number of cautions must be observed in interpreting these reports of temporal association. First, in some cases increase or decrease in resistance occurred independent of changes in drug usage;[40-42] in others, decreased prevalence of resistance occurred where drug usage increased.[43] Second, many of the studies showing temporal relationships describe epidemic periods. In these episodes, prevalence of the antibiotic-resistant epidemic strain decreased after changes in antibiotic use, but other epidemic control measures were put into effect concurrently. This makes it more difficult to attribute a causal role to altered antibiotic prescribing. Third, the resistant organisms that emerge do not necessarily persist.[55] Fourth, even a marked increase in resistance at a given institution may increase the level only to levels seen at other institutions many years ago.[56] Fifth, a relationship may be apparent for some organisms but not for others.[7,28,38,44]

Hospital areas with highest usage of antimicrobials have the highest prevalence of antibiotic-resistant bacteria. In many hospitals antibiotic-resistant organisms are most frequently encountered in special care units, and these are the areas where antimicrobial usage is most pervasive.[44,46] Certainly not all antimicrobial resistance orginates in these areas, but a dose-response pattern of concurrent association often is present.

Increasing likelihood of colonization or infection with resistant organisms occurs with increasing duration of exposure to antibiotics in the hospital.[57] The increased risk seems to be present whether or not the individual has been treated with antibiotics. Thus, it appears to be a second example of dose-response relationship.

Increasing dosage of antimicrobial leads to greater likelihood of superinfection or colonization with resistant organisms. This is best documented for the respiratory tract, and seems to hold better for some organisms than for others.[7] Yet, in general, a dose-response relationship seems to hold.

TABLE V. EXAMPLES OF ASSOCIATION BETWEEN ANTIMICROBIAL USE AND CHANGE IN RESISTANCE, 1980-1986

Drug	*Resistance in:*	*Reference(s)**
Aminoglycosides	Gram-negative aerobic bacilli	24,25, 27-44
	S. epidermidis	45
Beta-lactams	Enterobacter	46
	Gram-negative bacilli	18
	Gram-positive cocci	21
Methicillin	Coagulase-negative staphylococci	47
	Enterococci	48
Perfloxacin	*Ps. aeruginosa*	49
Trimethoprim	*E. coli*	50
Trimethoprim-sulfamethoxazole	Gram-negative aerobic bacilli	51
	Shigella flexneri	52
Multiple	*Salmonella typhi*	53
	Serratia marcescens	54

*Not necessarily comprehensive

A biologic model can be proposed to explain the relationship between the proposed cause and effect. Antimicrobial usage in hospitals is extensive, and antibiotics are present in the hospital environment as well. As a result, both patient and hospital employee are exposed to antimicrobials. Antibiotic therapy can produce marked effects on an individual's endogenous flora, and can select preferentially for organisms resistant to the drug. Hence, antimicrobial usage tends to insure that organisms resistant to antibiotics preferentially will be present in the hospital environment, and thus likely to be involved when and if spread or infection occurs. Note that this presumes no effect on attack rate of nosocomial infection; it is by determining the likely organisms rather than by increasing the frequency of occurrence that antibiotic use appears to exert its influence on nosocomial infection.

How Good Is The Evidence?

Given the problems with methods discussed above, none of the individual bits of data listed above establishes the relationship between antibiotics and resistance. However, taken as a whole, the above features satisfy many of the criteria that test the plausibility of proposed causal relationships (Table IV). The first two show antimicrobial usage to be a risk indicator for prevalence of resistance, and the next five suggest a causal link. Consistent association between the proposed cause and effect exists in several study popu-

lations. There exists a biologic gradient (dose-response relationship) in which more exposure to antibiotics leads to more resistance—three examples of this are given above. The time course is logical—the proposed cause (antimicrobial usage) precedes the proposed effect (changes in prevalence of resistance). Finally, a reasonable biologic model is present.

Thus, a substantial body of information exists to make likely a causal relationship between use of antimicrobial agents and prevalence of hospital organisms resistant to antibiotics.[7] The evidence is strong enough that the relationship recently has been recognized by a number of groups, including the Fogarty International Center of the National Institutes of Health,[1] the Alliance for the Prudent Use of Antibiotics,[53] and the World Health Organization.[58] Additionally, in a survey of members of the Infectious Diseases Society of America, 93% of 881 respondents indicated that they "strongly agreed" or "agreed" that antibiotic use in hospitals is a major cause of antibiotic resistance.[59]

It is unlikely, however, that a clear relationship between use and resistance can be established as a universal phenomenon. The data above indicate that this relationship may hold only for specific drugs, microorganisms, and hospital settings.

Questions For The Future

Given the link between the ways we use antimicrobials and the likelihood of resistance emerging, a number of issues deserve further examination.

The relative potential of an antimicrobial for triggering resistance will also have to be part of our evaluation of its value, but efficient methods for this are sadly lacking at present.[4,13] Development of such methods should be a high priority for researchers in this rapidly-advancing field.[60]

The biggest step that can be taken to minimize the risk that antimicrobial resistance will emerge is reducing the use of antimicrobials where quality of care will not be compromised. We still need effective and efficient systems to ensure that drugs are given only when needed and for the shortest duration possible.

The cost-effectiveness of antimicrobial use has become a current concern.[61] Decreasing overall antimicrobial use has been given special importance in today's prospective reimbursement system.[62] Particular emphasis has been placed on rational prescription in prophylaxis for surgery.[47] This new emphasis works to the advantage of those concerned about overuse of antimicrobials. Attempts to limit costs for unneeded prescriptions will help

at the same time to minimize the likelihood of antimicrobial resistance. However, the phenomenon of linkage of resistance factors makes it uncertain that decreased use will lead to a drop in prevalence of resistance to that drug.[13,20,21,25,36,46,56]

It has been suggested that "cycling" antimicrobials (substituting a new member of a drug family for drugs currently in use) might decrease the overall prevalence of resistance or at least resistance to other drugs in the same family.[4] A number of recent papers[24,27-31,34-38] have attempted to assess the effectiveness of this strategy. Most of these trials have substituted amikacin for other aminoglycosides in use in a hospital in hopes of reducing prevalence of resistance to other aminoglycosides (Table VI).

Several of these trials have produced apparent decreases in prevalence of resistance to gentamicin or tobramycin without increase in amikacin resistance. Nevertheless, these results must be interpreted with caution. In some trials, an increase in prevalence of amikacin resistance was seen during amikacin use,[30,36,37] and on occasion an increase in prevalence of amikacin resistance was noted when the drug had not been employed.[40] In countries where amikacin has been introduced into routine use, prevalence of resistance seems to have increased.[39] Even when no change was detected, it cannot be assumed that change would have occurred in a straight-line dose-response relationship. In fact, resistance to the aminoglycosides has not followed this pattern in the past. The interval between introduction of an antimicrobial into routine clinical use and appearance of resistant strains in hospital populations has varied markedly for different drug-organism pairs.[7,31] Occasionally, resistance has developed shortly after introduction of the drug, but more frequently a drug has been used for an appreciable period before resistance becomes prevalent.[10,44]

The major consideration in predicting whether or not "cycling" or substitution of antimicrobials might be effective is assessment of the organisms causing nosocomial infection in a given hospital and the types of resistance mechanisms present in these endogenous bacteria. There are certain settings in which substitution of a new drug has worked, and this step should be considered in the correct setting. Whether to make this attempt depends on several considerations: First, does a problem of resistance exist? In many hospitals resistant organisms appear to be little or no problem.[10-12] In view of the high cost of many of the alternative drugs, it makes no sense to introduce a new agent if no difficulty is being seen.[63] Second, is the problem hospital organism or group of organisms known to have responded to such

TABLE VI. CHANGES IN PREVALENCE OF RESISTANCE IN GRAM-NEGATIVE AEROBIC BACILLI ASSOCIATED WITH CHANGES IN USE OF AMINOGLYCOSIDE ANTIMICROBIALS IN SEVERAL STUDIES, 1980-1986

First author (reference)		*Change in use of:*			*Change in resistance to:*		
		*Gent**	*Tobr*	*Amik*	*Gent*	*Tobr*	*Amik*
Berk	24	D**	D	I	D	D	S
Yurosek	27	D		I	D		S
Moody	28	D		I	D		S
Wielunsky	29	D		I	D		
Cross	30	I	S	I	I	I	I
Betts	31	D		I	D	D	S
Saravolatz	34						
Period 1		D		I	D		
Period 2		I		D	I		
Shulman	35	D	D	I	S	S	S
Levine	36	S	I	I	S	S	I
Gerding	37						
14 VA Hosps		D	D	I	D	D	I
Mpls VA Period 1		D	D	I	D	D	S
Mpls VA Period 2		I		D	I	I	S
Mpls VA Period 3		D		I	D	D	D
Young	38						
Period 1		D		I	D		S
Period 2		I		D	I		I

*Gent = Gentamicin, Tobr = Tobramycin, Amik = Amikacin
**D = decrease, I = increase, S = remained stable. No entry = data not available or drug not used

tactics in the past? Some responses have been organism-specific (Table V). Substitution may not be as effective as limiting total prescriptions and duration of use for a given drug—especially if the resistance is plasmid-mediated and linked to other resistance factors.[64] Third, what is the goal of the substitution? A goal of decreasing the selective pressure favoring an epidemic hospital organism seems potentially achievable. However, the value of introducing one drug in an attempt to decrease prevalence of resistance to a second drug must be questioned if levels of resistance to the second drug rise again when its use is reinstated.[34,37] Further information is needed as to the cost effectiveness of such programs.

Control of antimicrobial use or change in the drugs in use are not the only factors involved in decreasing antimicrobial resistance. This is demonstrated well by Saravolatz and colleagues,[34] who found that restriction of aminoglycoside usage did little to slow an outbreak of resistant organisms in the hospital; the problem persisted until additional infection control procedures were implemented. Similar findings were noted by Gaines et al.[33] Antimicrobial usage review and/or control is but one facet of the attack on resistant hospital organisms. New approaches to control will depend on studies defining the relative importance of emergent resistance compared with impact of exogenously-acquired strains.[25]

SUMMARY

Organisms causing nosocomial infection frequently are resistant to antimicrobial agents. Studies of the reasons for this have been hindered by methodologic difficulties. Lack of standard definitions of resistance and selection biases have been common. Studies have failed to control for such confounding variables as the prevalence of host defense abnormality in hospitalized patients, varying use of procedures and instruments, and inherent characteristics of the infecting organism. Despite these problems, epidemiologic criteria for a causal relationship between antibiotic usage and resistance of hospital organisms is supported by new data of several types. Existence of such a cause and effect relationship forces us to develop methods to assess the potential for newer antimicrobials to trigger resistance and to improve measures to prevent spread of resistant organisms within the hospital. Antimicrobial usage must be reduced whenever such decrease will not compromise quality of care, but such reduction may not decrease the prevalence of resistance to the drug. The value of rotation or cycling of antimicrobials will depend on local patterns of resistant organisms, prevalence of specific resistance mechanisms in a given population of nosocomial organisms, and the goals set for such change in prescribing practices.

REFERENCES

1. Burke, J.P. and Levy, S.B.: Summary report on worldwide antibiotic resistance: international task forces on antibiotic use. *Rev. Infect. Dis.* 7:560-64, 1985.
2. Kunin, C.M.: The responsibility of the infectious disease community for the optimal use of antimicrobial agents. *J. Infect. Dis. 151*:388-98, 1985.
3. McGowan, J.E., Jr.: Changing etiology of nosocomial bacteremia and fungemia and other hospital-acquired infections. *Rev. Infect. Dis.* 7:S357-70, 1985.
4. Thornsberry, C.: Personal communication.
5. Baum, C. et al.: Drug use and expenditures in 1982. *J.A.M.A. 253*:382-86, 1985.

6. Isenberg, H.D. and Berkman, J.I.: The role of drug-resistant and drug-selected bacteria in nosocomial disease. *Ann. N.Y. Acad. Sci. 182*:52-58, 1971.
7. McGowan, J.E., Jr.: Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev. Infect. Dis. 5*:1033-48, 1983.
8. Haley, R.W., Tenney, J.H., Lindsey, J.O. II, et al.: How frequent are outbreaks of nosocomial infection in community hospitals? *Infect. Control 6*:233-36, 1985.
9. Dixon, R.E.: Epidemiology of Drug Resistance in Hospitals. In: *Drug-Inactivating Enzymes and Antibiotic Resistance*, Mitsuhashi, S., Rosival, L., and Kremery, V., editors. New York, Springer-Verlag, pp. 349-60, 1975.
10. Magnussen, C.R. and Jacobson, M.T.: Longitudinal analysis of endemic gentamicin and tobramycin-resistant Gram-negative bacilli in a community hospital. *Infect. Control 5*:88-92, 1984.
11. Gardner, D.A. and Lorian, V.: Bacterial susceptibility to antibiotics remains virtually stable. *Antimicrob. Newsletter 2*:9-13, 1985.
12. Barry A: Bacterial antibiotic resistance before and after clinical application in the United States. *Bull. N.Y. Acad. Med. 63*:217-30, 1987.
13. Sanders, C.C. and Sanders, W.E., Jr.: Microbial resistance to newer generation beta-lactam antibiotics: clinical and laboratory implications. *J. Infect. Dis. 151*:399-46, 1985.
14. Freeman, J. and McGowan, J.E., Jr.: Methodologic issues in hospital epidemiology. I. Rates, case-finding, and interpretation. *Rev. Infect. Dis. 3*:658-67, 1981.
15. Neu, H.C.: Symposium—The patient at risk for infection: a summary. *Am. J. Med. 76*:240-43, 1984.
16. Warren, J.W.: Providencia stuartii: a common cause of antibiotic-resistant bacteriuria in patients with long-term indwelling catheters. *Rev. Infect. Dis. 8*:61-67, 1986.
17. Rice, R.J., Biddle, J.W., Jean Louis, Y.A., et al.: Chromosomally mediated resistance in Neisseria gonorrhoeae in the United States: results of surveillance and reporting, 1983-1984. *J. Infect. Dis. 153*:340-45, 1986.
18. McCue, J.D.: Cefoxitin resistance in community-acquired Gram-negative bacillary bacteremia. *Arch. Intern. Med. 145*:834-36, 1985.
19. Davenport, D.S., Massanari, R.M., Pfaller, M.A., et al.: Usefulness of a test for slime production as a marker for clinically significant infections with coagulase-negative staphylococci. *J. Infect. Dis. 153*:332-39, 1986.
20. Schaberg, D.R., Power, G., Betzold, J., and Forbes, B.A.: Conjugative R plasmids in antimicrobial resistance of Staphylococcus aureus causing nosocomial infections. *J. Infect. Dis. 152*:43-49, 1985.
21. Jones, R.N. and Thornsberry, C.: Gram-positive superinfections: a consequence of modern beta-lactam therapy. *Antimicrob. Newsletter 2*:17-23, 1985.
22. Price, D.J.E. and Sleigh, J.D.: Control of infection due to Klebsiella aerogenes in a neurosurgical unit by withdrawal of all antibiotics. *Lancet 2*:1213-15, 1970.
23. Graham, D.R., Clegg, H.W., II, Anderson, R.L., et al.: Gentamicin treatment associated with later nosocomial gentamicin-resistant Serratia marcescens infections. *Infect. Control 2*:31-37, 1981.
24. Berk, S.L., Alvarez, S., Ortega, G., et al.: Clinical and microbiologic consequences of amikacin use during a 42-month period. *Arch. Intern. Med. 146*:538-41, 1986.
25. Olson, B., Weinstein, R.A., Nathan, C., et al.: Occult aminoglycoside resistance in Pseudomonas aeruginosa: epidemiology and implications for therapy and control. *J. Infect. Dis. 152*:769-74, 1985.
26. Finland, M.: Emergence of antibiotic resistance in hospitals 1935-1975. *Rev. Infect. Dis. 1*:4-21, 1979.
27. Yurasek, M.C., Wang, W.L., and Mostow, S.R.: Reduction in gentamicin resistance among Gram-negative bacilli with the exclusive use of amikacin. *Clin. Res. 29*:92A, 1981.
28. Moody, M.M., deJong, C.A., and

Schimpff, S.C.: Long term amikacin use: effects on aminoglycoside susceptibility patterns of Gram-negative bacilli. *J.A.M.A. 248*:1199-1202, 1982.
29. Wielunsky, E., Drucker, E., and Cohen, T.: Replacement of gentamicin by amikacin as a means of decreasing gentamicin resistance of Gram-negative rods in a neonatal intensive care unit. *Isr. J. Med. Sci. 19*:1006-08, 1983.
30. Cross, A.S., Opal, S., and Kopecko, D.J.: Progressive increase in antibiotic resistance of Gram-negative bacterial isolates: Walter Reed Hospital, 1976 to 1980: specific analysis of gentamicin, tobramycin, and amikacin resistance. *Arch. Intern. Med. 143*:2075-80, 1983.
31. Betts, R.F., Valenti, W.M., and Chapman, S.W.: Five-year surveillance of aminoglycoside usage in a university hospital. *Ann. Intern. Med. 100*:219-22, 1984.
32. Huovinen, P., Gronroos, P., and Herva, E.: Aminoglycoside resistance among blood culture isolates. *J. Clin. Microbiol. 20*:65-69, 1984.
33. Gaynes, R.P., Weinstein, R.A., Smith, J., et al.: Control of aminoglycoside resistance by barrier precautions. *Infect. Control 4*:221-24, 1983.
34. Saravolatz, L.D., Arking, L., and Pohlod, D.: An outbreak of gentamicin-resistant Klebsiella pneumoniae: analysis of control measures. *Infect. Control 5*:79-84, 1984.
35. Shulman, S.T. and Yogev, R.: Treatment of pediatric infections with amikacin as a first-line aminoglycoside. *Am. J. Med. 79*:43-50, 1985.
36. Levine, J.F., Maslow, M.J., and Leibowitz, R.E.: Amikacin-resistant gram-negative bacilli: correlation of occurrence with amikacin use. *J. Infect. Dis. 151*:295-300, 1985.
37. Gerding, D.N. and Larson, T.A.: Aminoglycoside resistance in Gram-negative bacilli during increased amikacin use. *Am. J. Med. 79*:1-7, 1985.
38. Young, E.Y., Sewell, C.M., Koza, M.A., and Clarridge, J.E.: Antibiotic resistance patterns during aminoglycoside restriction. *Am. J. Med. Sci. 290*:223-27, 1985.
39. Shimizu, K., Kumada, T., Hsieh, W., et al.: Comparison of aminoglycoside resistance patterns in Japan, Formosa, and Korea, Chile, and the United States. *Antimicrob. Agents Chemother. 28*:282-88, 1985.
40. Bryan, C.S., Parker, E., Schoenlein, P.V., et al.: Plasmid-mediated antibiotic resistance in a changing hospital environment: efficacy of control measures. *Am. J. Infect. Control 8*:65-71, 1980.
41. John, J.F., Jr., Rubens, C. E., and Farrar, W.E., Jr: Characteristics of gentamicin resistance in nosocomial infections. *Am. J. Med. Sci. 279*:25-30, 1980.
42. Weinstein, R.A., Nathan, C., Gruensfelder, R., and Kabins, S.A.: Endemic aminoglycoside resistance in Gram-negative bacilli: epidemiology and mechanism. *J. Infect. Dis. 141*:338-45, 1980.
43. Lane, M. M., Parker, D. E., and Flournoy, D.J.: Trends in bacterial susceptibility to antimicrobial agents. *Chemotherapy 31*:433-39, 1985.
44. Daschner, F., Langmaak, H., and Wiedemann, B.: Antibiotic resistance in intensive care unit areas. *Infect. Control 4*:382-87, 1983.
45. Riben, P.D., Horsman, G.B., Rayner, E., et al.: Emergence of tobramycin-resistant S. epidermidis possessing aminoglycoside modifying enzymes and bacteremic superinfection during empiric therapy of febrile neutropenic episodes. *Clin. Invest. Med. 8*:272-85, 1985.
46. Weinstein, R.A.: Endemic emergence of cephalosporin-resistant Enterobacter: relation to prior therapy. *Infect Control 7*:120-23, 1986.
47. Maki, D. and Stevens, J.: Nosocomial colonization of cardiovascular surgery and cardiology patients by methicillin-resistant coagulase-negative staphylococcus. *Am. J. Infect. Control 12*:257-58, 1984.
48. Crossley, K. B. and Ross, J.: Colonization of hospitalized patients by Staphylococcus aureus, Staphylococcus epidermidis, and enterococci. *J. Hosp. Infect. 6*:179-86, 1985.
49. Van der Auwera, P., Klastersky, J., Lieppe, S., et al.: Bactericidal activity

and killing rate of serum from volunteers receiving perfloxacin alone or in combination with amikacin. *Antimicrob. Agents Chemother. 29*:230-34, 1986.
50. Huovinen, P., Pulkkinen, L., Helin, H., et al.: Emergence of trimethoprim resistance in relation to drug consumption in a Finnish hospital from 1971 through 1984. *Antimicrob. Agents Chemother. 2*:73-76, 1986.
51. Murray, B.E., Alvarado, T., Kim, K., et al.: Increasing resistance to trimethoprim-sulfamethoxazole among isolates of Escherichia coli in developing countries. *J. Infect. Dis. 152*:1107-13, 1985.
52. Shahid, N.S., Rahaman, M., Haider, K., et al.: Changing pattern of resistant Shiga bacillus (Shigella dysenteriae type 1) and Shigella flexneri in Bangladesh. *J. Infect. Dis. 152*:1114-19, 1985.
53. Farrar, W.E.: Antibiotic resistance in developing countries. *J. Infect. Dis. 152*:1103-06, 1985.
54. Sanders, C.C. and Watanakunakorn, C.: Emergence of resistance to beta-lactams, aminoglycosides, and quinolones during combination therapy for infection due to Serratia marcescens. *J. Infect. Dis. 153*:617-19, 1986.
55. Mickelsen, P.A., Plorde, J.J., Gordon, K.P., et al.: Instability of antibiotic resistance in a strain of Staphylococcus epidermidis isolated from an outbreak of prosthetic valve endocarditis. *J. Infect. Dis. 152*:50-58, 1985.
56. Cherubin, C.E., Eng, R.H.K., Dabernat, H., and Lareng, M.B.: Comparison of antibiotic resistance of Gram-negative bacilli with beta-lactam and aminoglycoside antibiotics. *Diag. Microbiol. Infect. Dis. 4*:153-59, 1986.
57. Goldmann, D.A.: Bacterial colonization and infection in the neonate. *Am. J. Med. 70*:417-22, 1981.
58. World Health Organization Scientific Working Group on Antimicrobial Resistance: Control of antibiotic-resistant bacteria: memorandum from a WHO meeting. *Am. J. Hosp. Pharm. 41*:1329-37, 1984.
59. Kunin, C.M. and Chambers, S.: Responsibility of the infectious disease community for optimal use of antibiotics: views of the membership of the Infectious Diseases Society of America. *Rev. Infect Dis. 7*:547-59, 1985.
60. Jorgensen, J.H.: Susceptibility test methods which may be able to predict the emergence of resistance to newer beta-lactam antibiotics. *Chemioterapia 4*:7-13, 1985.
61. Neu, H.C.: Antimicrobial activity, bacterial resistance, and antimicrobial pharmacology: is it possible to use new agents cost-effectively? *Am. J. Med. 77*:17-22, 1985.
62. Quintiliani, R., Klimek, J.J., and Nightingale, C.H.: Restriction policies for therapy with combination antibiotics. *J. Infect. Dis. 153*:645-47, 1986.
63. Manu, P.: Empiric use of aminoglycosides in hospitals. *Ann. Intern. Med. 100*:919, 1984.
64. Woloj, M., Tolmasky, M.E., Roberts, M.C., and Crosa, J.H.: Plasmid-encoded amikacin resistance in multiresistant strains of Klebsiella pneumoniae isolated from neonates with meningitis. *Antimicrob. Agents Chemother. 29*:315-19, 1986.